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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/602,272	02/16/1996	MICHAEL J. ELLIOTT	KIR96-01	4297

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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	08/602,272	ELLIOTT ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6, 9, 10, 12-15, 51 and 53 a* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *51* is/are allowed.

6)☒ Claim(s) *6, 9, 10, 12-15, and 53 a* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 11, 2008 has been entered. It is noted that the claims set submitted on November 11, 2008 is identical to the claim set submitted on October 8, 2008 which has been entered as indicated in the Advisory Action of November 4, 2008. However, applicants has submitted further arguments against the rejections of record which will be addressed.

Claims 6, 9, 10, 12-15, 51 and 53 are pending and under consideration.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of claim 6 rejected under 35 U.S.C. 103(a) as being unpatentable over the abstract of Strieter et al (Critical Care Medicine, 1993, 21(10 suppl):S447-S463) in view of Le et al (WO 92/16553) is maintained for reasons of record.

The abstract of Strieter et al teaches that a synthesis of literature data from 1975 indicates that TNF influences the outcome of ischemia-reperfusion injury, and that administration of anti-TNF antibodies may limit organ damage induced by TNF and reduce mortality rates Strieter et al do not specifically teach the use of an anti-human TNF antibody which is a monoclonal antibody.

Le et al teach the monoclonal antibody A2 which binds to human TNF alpha as stated in the instant specification (page 8, lines 9-22). Le et al teach a method for treating a subject having a pathology mediated by TNFa comprising administering to said subject a therapeutic amount of a monoclonal antibody to human TNF, wherein said pathology is selected from sepsis syndrome, cachexia, circulatory collapse and shock resulting from acute or chronic bacterial infection, a bacterial infection, a viral infection, a fungal infection, systemic lupus erythematosus, rheumatoid arthritis, alcohol-induced hepatitis, a chronic inflammatory pathology, a vascular inflammatory pathology, a graft-versus-host pathology, Kaisaki 5 pathology and a malignant pathology (claims 32 and 40). Le et al do not specifically teach ischemia-reperfusion injury as a TNF alpha mediated pathology. However, Strieter et al teach that ischemia-reperfusion injury is a TNF a mediated pathology.

It would have been prima facie obvious to use the method of Le et al for the treatment of ischemia-reperfusion injury in humans. One of skill in the art would have been motivate to do so by the suggestion of Strieter et al that TNF a is a mediator of injury in ischemia-reperfusion.

Applicant has previously argued that the abstract discloses only data relevant to the pathogenesis of the human systemic inflammatory response syndrome secondary to infection, rather than the treatment of a thrombotic disorder. This was considered but not found persuasive. The abstract clearly discusses the influence of TNF alpha in ischemia-reperfusion injury which fulfills the limitation of claim 6 as it is drawn to an "ischemic event". Applicant further argued that the abstract is not enabling for claim 6. This was been considered but not found persuasive. The use of antibodies for the treatment of human disease was well-known in

the art as of the filing date of the instant application. It is noted that claim 6 requires only the administration of therapeutically effective amount of anti-human tumor necrosis factor monoclonal antibody to an individual in order to treat an ischemic event. The examiner maintains that the treatment of ischemia-reperfusion injury falls within the scope of an ischemic event. Applicants argument that the instant claimed method is not intended for use secondary to infection is therefore moot. Further, it would be within the purview of one of skill in the art to make an anti-human TNF monoclonal antibody to treat human pathologies mediated by TNF a as taught by Le et al. Applicant argues that Streiter et al do not disclose or suggest that the administration of anti-TNF antibodies will positively treat a subject suffering from a thrombolytic disorder. This has been considered but not found persuasive. The standard for 103(a) is a reasonable expectation of success. It is noted that Le e al provides an improvement in the art by the administration of high affinity antibodies which bind to THF alpha (claim 1), and further, a chimeric mouse-human antibody designed to reduce anti-HAMA response in human patients. Applicant argued that the state of the art was unreliable because of the result of six clinical trials where none o of the administered therapies improved the survival of the subjects. This was considered but not found persuasive. Firstly it appears that the studies used the Bay-X-1351 antibody and therefore none of the studies used the cA2 antibody which is a chimeric high affinity antibody that binds to human TNF. Le et al teaches that said antibody is an improvement over the prior art because it overcomes the problems of murine antibody immunogenicity and provides increased neutralization activity (page 6, line 35 to page 7, line 17). Applicant argued that the abstract of Streiter et al provides incorrect information in light of the review of Freeman and Natanson (Current Opinion in Critical Care, 1995, vol. 1, pp. 349-357) which reports negative results for the administration of anti-TNF antibodies to patients suffering from septic shock. This was considered but not found persuasive. Streiter et al was reviewing a wide range of articles on Medline to identify pertinent human and animal studies that focused on the mechanism of action of TNF and potential uses of anti-TNF therapies. Results from the clinical studies reported by Freeman and Natanson are limited instances of failure to prolong survival. Clearly, Le et al discusses the problems of the prior art with regard to the development of anti-HAMA response which decreases the efficacy of the administered antibody, and therefore the

improvement to the antibody taught by Le has overcome the problems associated with the prior art antibodies.

Applicant now argues that the rejection of amended claim 6 is overcome. Applicant has provided no reasons why this is so, and has submitted an amendment after final which simply replaced the word "alpha" with the Greek Letter alpha. applicant argues that the disclosure by Freedman and Natson provide demonstrate a lack of predictability in the art because of the conclusion that the administration of the three prior art antibodies showed no beneficial effects. It is noted that, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). The prior art clearly recognized the need for neutralizing THF alpha in illnesses associated with the production of TNF-alpha. Freedman and Natson review the prior art regarding clinical trials in sepsis and septic shock and cite two articles in which the use of anti-TNF alpha antibodies which were not the antibodies of Le et al failed to provide benefit (Abraham et al, JAMA, 1995, Vol. 273, pp. 934-941 and Fisher, et al , Critical Care Medicine, 1993, Vol. 21, pp. 318-327). It is noted that the treatment of septic shock includes the treatment of a patient suffering from an infection wherein said patients are fighting the infection and have an exaggerated immune response therefrom. This is not the case with patients being treated for ischemia-reperfusion injury.. Further the antibodies used by Abraham et al and Fisher et al do not include the antibody of Le et al

Results from the clinical studies reported by Freeman and Natanson are limited instances of failure to prolong survival. Clearly, Le et al discusses the problems of the prior art with regard to the development of anti-HAMA response which decreases the efficacy of the administered antibody, and therefore the improvement to the antibody taught by Le et al, that of decreased immunogenicity and increased neutralization activity, has overcome the problems associated with the prior art antibodies.

The rejection of claims 6, 9, 10, 12-15 and 53 under 35 U.S.C. 103(a) as being unpatentable over Le et al (US 5,656,272) in view of Bender et al (U.S. 5,317,019) is maintained for reasons of record.

Le et al teach a method for treating a TNFalpha mediated disease in a human comprising the administration of a chimeric anti-TNF antibody which bind to residues 87-108 and 59-80 in human TNF and the cA2 antibody (column 5, lines 36-47 and column 7, lines 10-25). Le et al do not teach the treatment of a TNFalpha mediated disease which is myocardial infarction or stroke by the administration of the cA2 antibody..

Bender et al teach that tissue injury associated with myocardial infarction and stoke is mediated by TNF (column 21, lines 20-25).

It would have been prima facie obvious at the time the claimed invention was made to substitute myocardial infarction or stoke for the TNFalpha mediated disease as taught by Le et al. One of skill in the art would have been motivated to do so by the teachings of Bender which identify myocardial infarction and stroke and TNFalpha mediated diseases. Further, the cA2 antibody would have the property of competitively inhibiting the binding of TNFalpha to cA2, thus fulfilling the limitation of claim 15

Applicant has previously agued that the method of Bender et al is unlike that of Le et al in that compounds are administered to inhibit the production of TNF rather than the administration of antibodies. Applicant argued that one of skill in the art would not have combined the two references because each reference target TNF differently. This has been considered but not found persuasive. It is especially noted that Le et al teach neutralizing monoclonal antibodies to human TNF alpha, and that the neutralization of said TNF alpha can provide a therapeutic effect to patients suffering from TNF mediated pathologies. Bender et al is relied upon for the nexus between TNF and myocardial infarction or stroke. The demonstration that the elimination or decrease of TNF production by certain drugs does not teach against the notion of substituting a neutralizing antibody because both methods are targeting a decrease in TNF: one method by neutralization and the other by inhibition of production. One of skill in the art would readily see that the outcome of reducing the TNF by administering the neutralizing antibody of Le et al would have a reasonable expectation of success.

Applicant again argues that the examiner has not provided a rational for the discounting of the teachings of Freeman and Natanson. Applicant is referred to the text under the rejection over the abstract of Strieter et al (Critical Care Medicine, 1993, 21(10 suppl):S447-S463) in view of Le et al (WO 92/16553), above. Applicant maintains that the disclosure of Freeman and Nanatson is not a limited instance. The examiner maintains that not only are the anti-TNF antibodies used in the works cited by Freeman and Nanatson different from the anti-TNF alpha antibody of Le et al, the disease being treated, sepsis, involves a different mediation by the endogenous immune response than the instant diseases of myocardial infarction or stroke, therefore the impact of neutralization or partial neutralization of TNF alpha on overall patient survival within the context of sepsis and infection may not be as significant with respect to overall patient survival as the impact of high TNF alpha neutralization using the chimeric anti-TNF alpha antibody of Le et al in the context of stroke or myocardial infarction. Applicant now argues that the amendments to claims 6, 9, 10, 12-15 and 53 are such that the above rejection is moot. The examiner wonders why this is so, because said amendments are not substantive and encompass only changes which further specify that the antibody includes an antigen-binding fragment thereof, or the substitution of the word "alpha" with the Greek letter. Applicant argues that at most Bender suggests that TNF is a likely mediator of "myocardial infarction, stoke and circulatory shock". applicant concludes that one of skill in the art would not have concluded that Bender et al provided a nexus between TNF alpha and myocardial infarction or stroke. This has been considered but not found persuasive. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the suggestion by Bender et al that TNF-alpha is a likely mediator provide a reasonable basis for success.

The rejection of claims 6, 9, 10, 12-15 and 53 under 35 U.S.C. 103(a) as being unpatentable over Le et al (US 5,656,272) and Bender et al (U.S. 5,317,019) as applied to claims 6, 9, 10, 12-15 and 53, above, and in further view of Naughton et al (U.S. 5,863,531) is maintained for reasons of record.

Claim 6 further comprises the thrombotic disorder of thromboembolism.

Naughton et al teach that the presence of anti-TNF antibodies can prevent thromboembolism (column 5, lines 4-12).

It would have been prima facie obvious to substitute thromboembolism for the TNF mediated diseases taught by Bender et al by using the antibodies of Le et al. One of skill in the art would have been motivated to do so by the suggestion of Naughton et al that thromboembolism is a TNF-mediated disease

Applicant has previously argued that Naughton et al disclose a stromal-cell based three dimensional system which in no way is related to either the Le et al disclosure or the Bender et al disclosure and that Naughton et al do not disclose any method of treating any disorder relating to TNF or preventing the production of TNF. This was considered but not found persuasive. Naughton et al teach the genetic engineering of stromal cells for vascular grafts, wherein said stromal cells express "peptides or polypeptides corresponding to the idiotype of neutralizing antibodies for tumor necrosis factor" (column 5, lines 10-12). Naughton et al teach that said genetic engineering provides for reduced risk of thromboembolism (column 5, lines 2-4).

Applicant now argues that Naughton et al does not disclose the anti-TNF-alpha antibody of the instant claims can prevent thromboembolism. This has been considered but not found persuasive. Naughton et al suggests that neutralizing antibodies can be used to prevent thromboembolism, and as such is relied upon for this suggestion. Naughton et al is not relied upon for a written description of the antibodies. Clearly the rejection relies upon the description of the chimeric antibody of Le et al to provide an anti-TNF antibody with high neutralizing activity and lowered immunogenicity.

Claim 51 is free of the art.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Karen A Canella/
Primary Examiner, Art Unit 1643